

Pesticides and Animal Health

- Adverse Effects and Drug/Chemical Residues

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Veterinary Approvals

FDA Approved: Spot-On and Pour-On Formulations

EPA Registered: Spot-On and Pour-On Formulations



US FDA

Ivermectin (Ivomec®)

Selamectin (Revolution®)

Fipronil (Frontline®, TopSpot®)

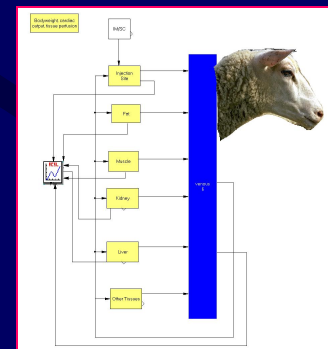
US EPA

Permethrin

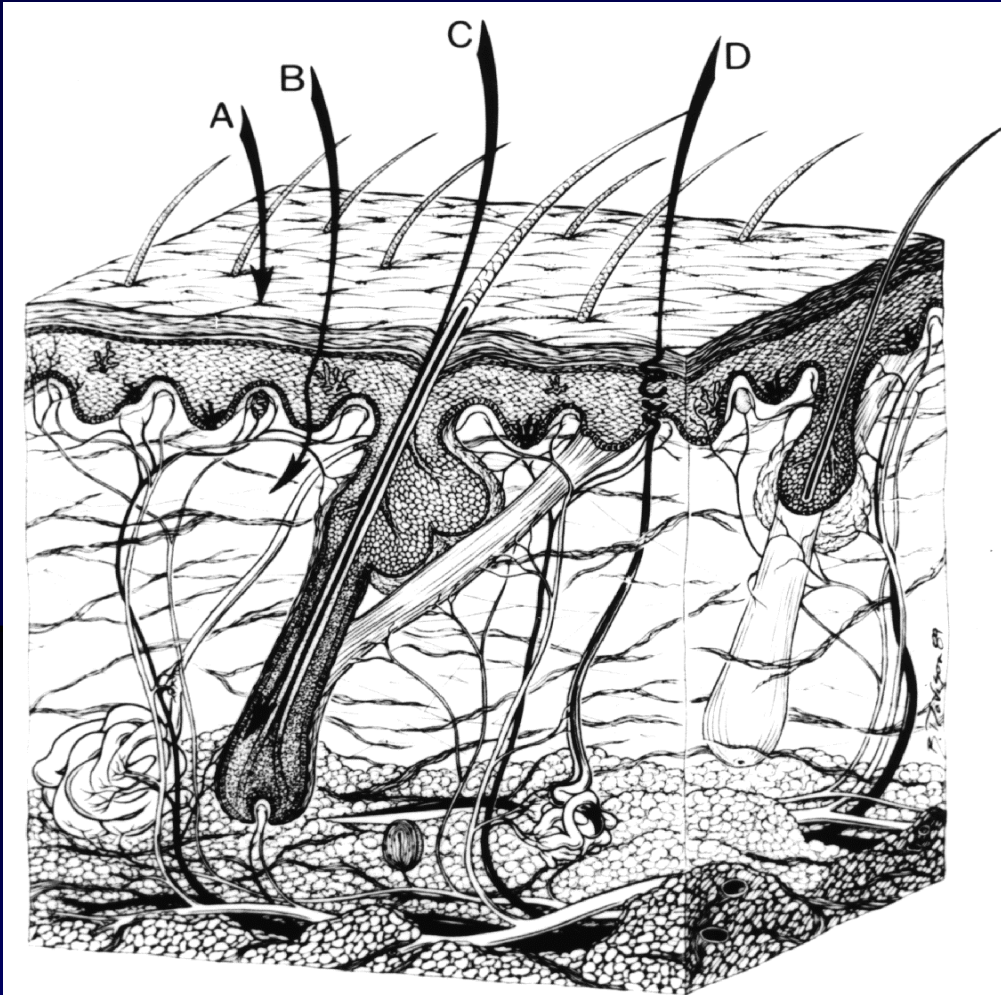
Imidacloprid (Advantage)

Outline of Presentation

- **Dermal Absorption Basics**
 - **How are these drugs/insecticides absorbed? Spp Diff?**
- **Once absorbed, what are the adverse effects of insecticides in veterinary species?**
- **Can there be Residues in meat and milk if livestock species are treated with these drugs?**
- **FARAD Cases and their resolution**
- **Summary and Challenges**

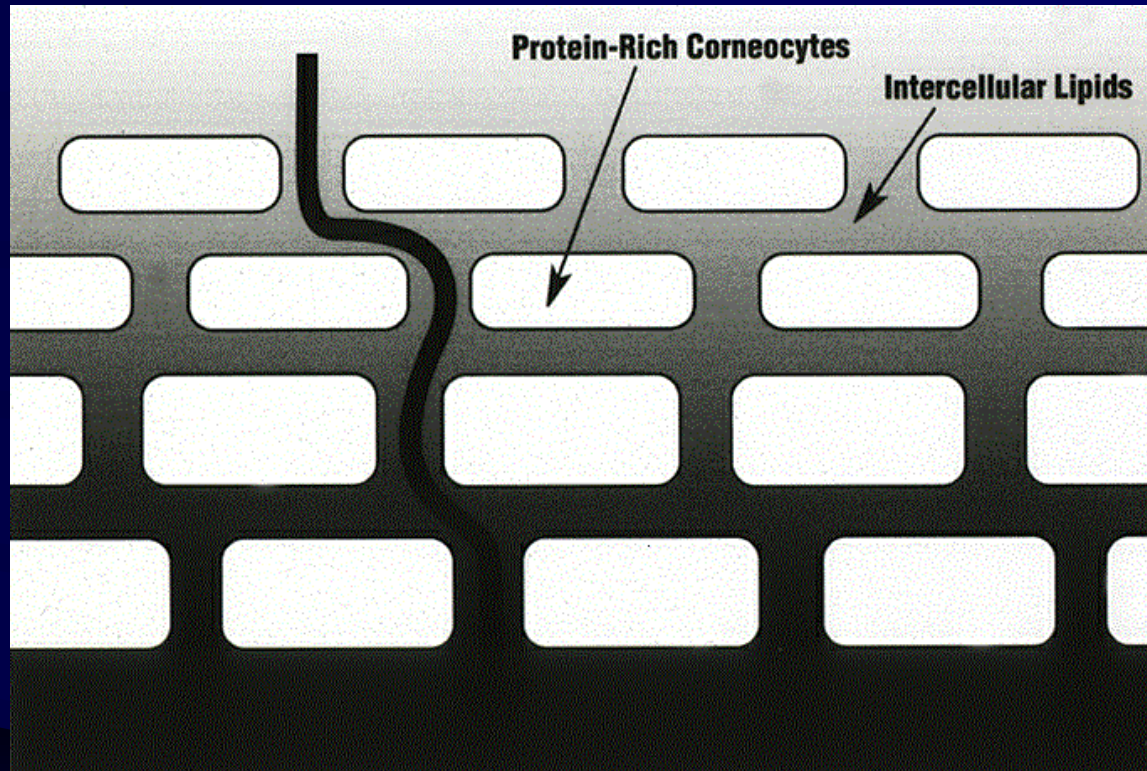


Possible Routes of Absorption



- A.- intercellular
- B.- transcellular
- C.- intrafollicular
- D.- via sweat ducts

Brick & Mortar Model



What is the objective of your drug/insecticide therapy?

Does it require systemic absorption?

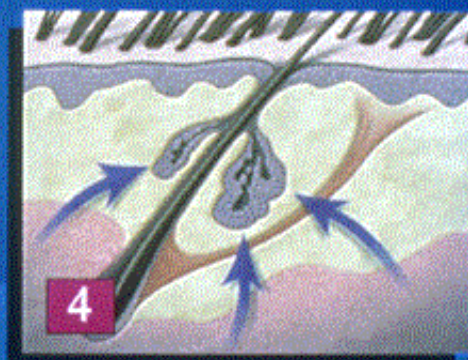
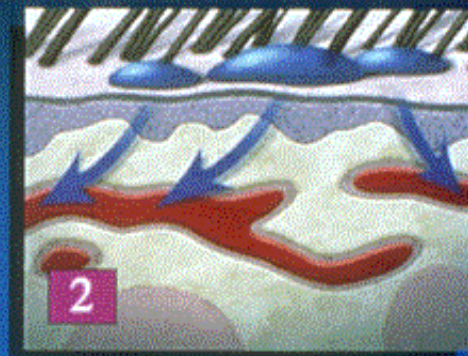
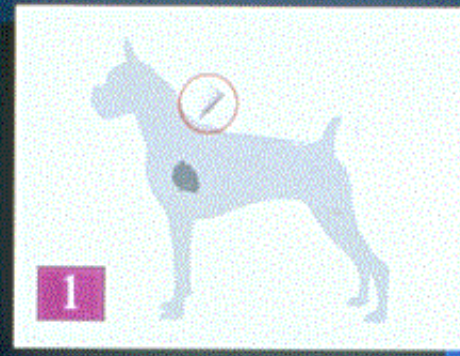
Does it require local skin distribution?

Differences in Drug Distribution

Avermectins vs. Neonicotinoids vs. Fipronil vs Pyrethroids

Avermectins (e.g., Selamectin)

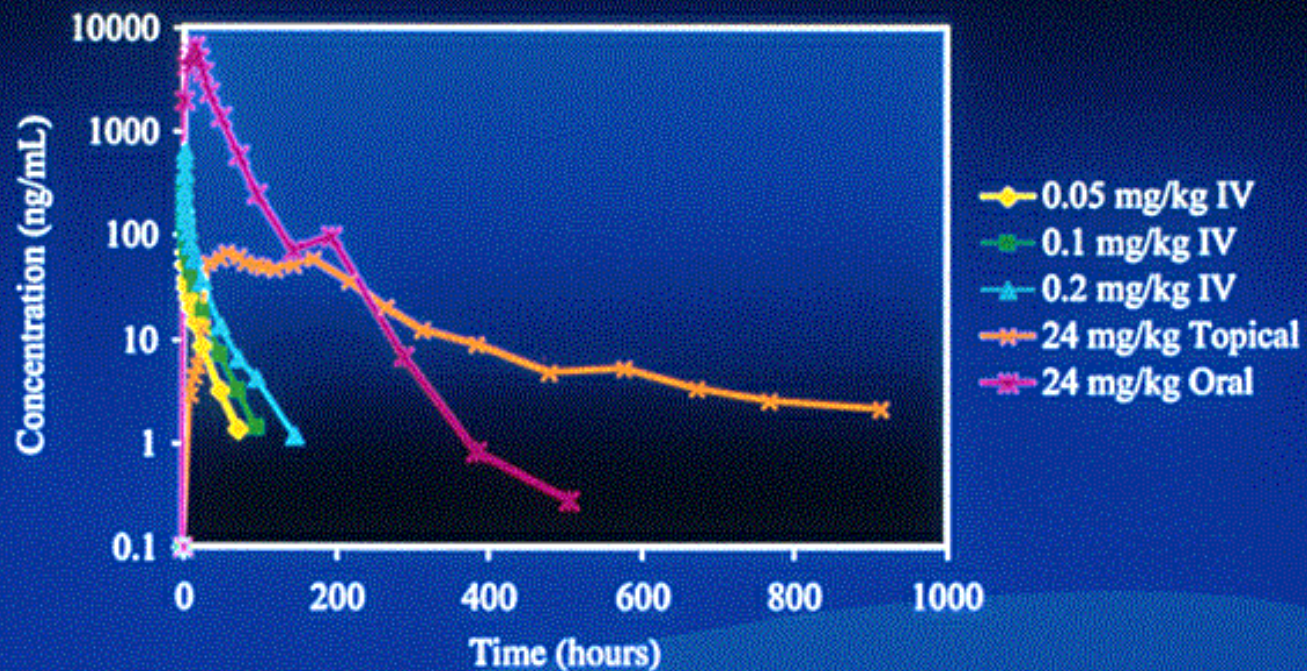
Pharmacokinetics



Why you also need to be cautious

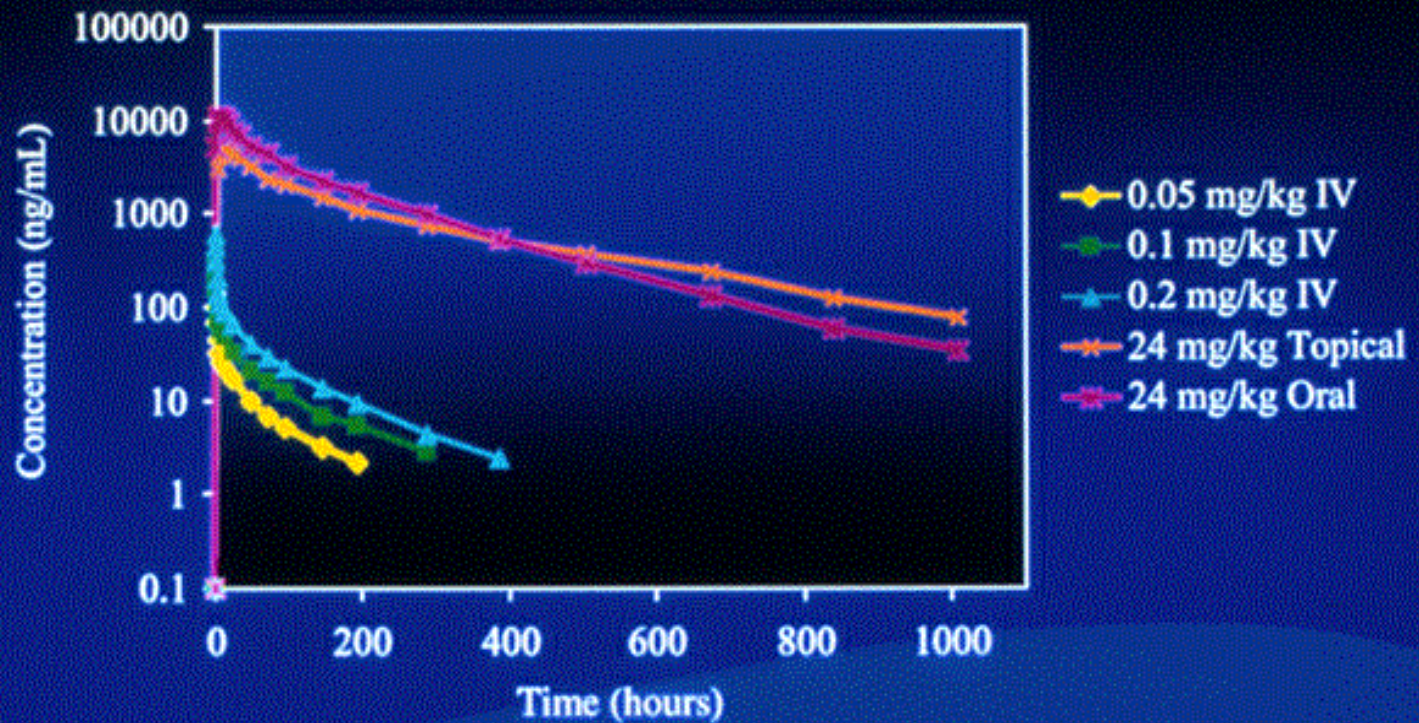
The PK of avermectins (ivermectin, selamectin, etc) is route specific.

Pharmacokinetics Results – Dogs



Selamectin

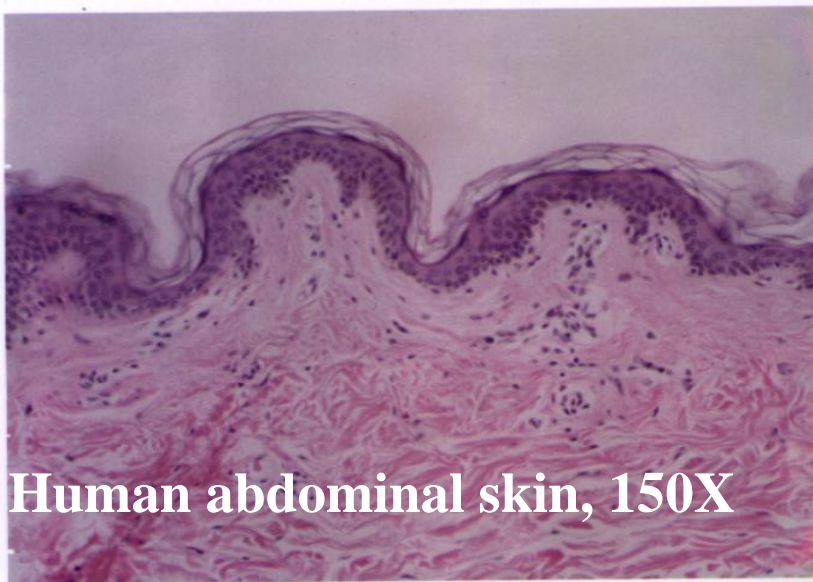
Pharmacokinetics Results – Cats



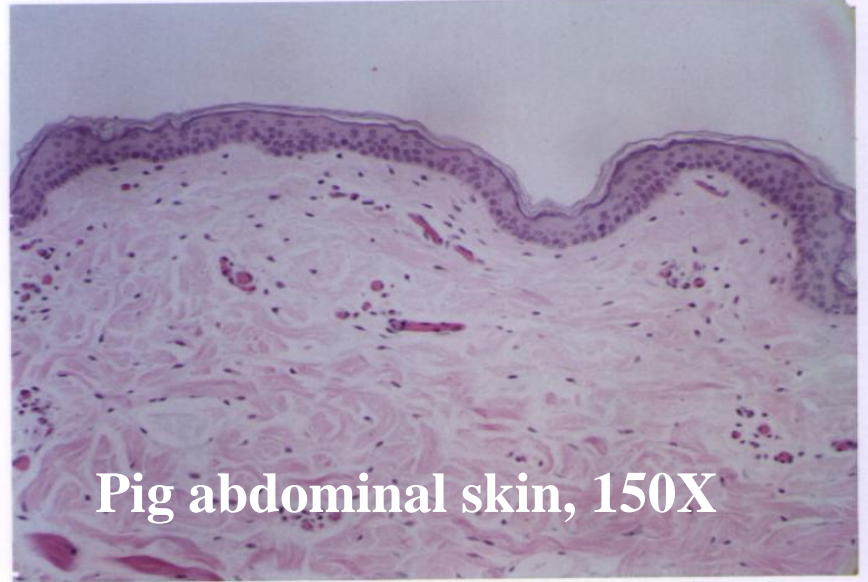
What is the Ideal Animal Model for Human Skin?

Many dermal absorption studies utilize porcine skin because of demonstrated similarities in:

- Structure
- Function
- Lipid composition



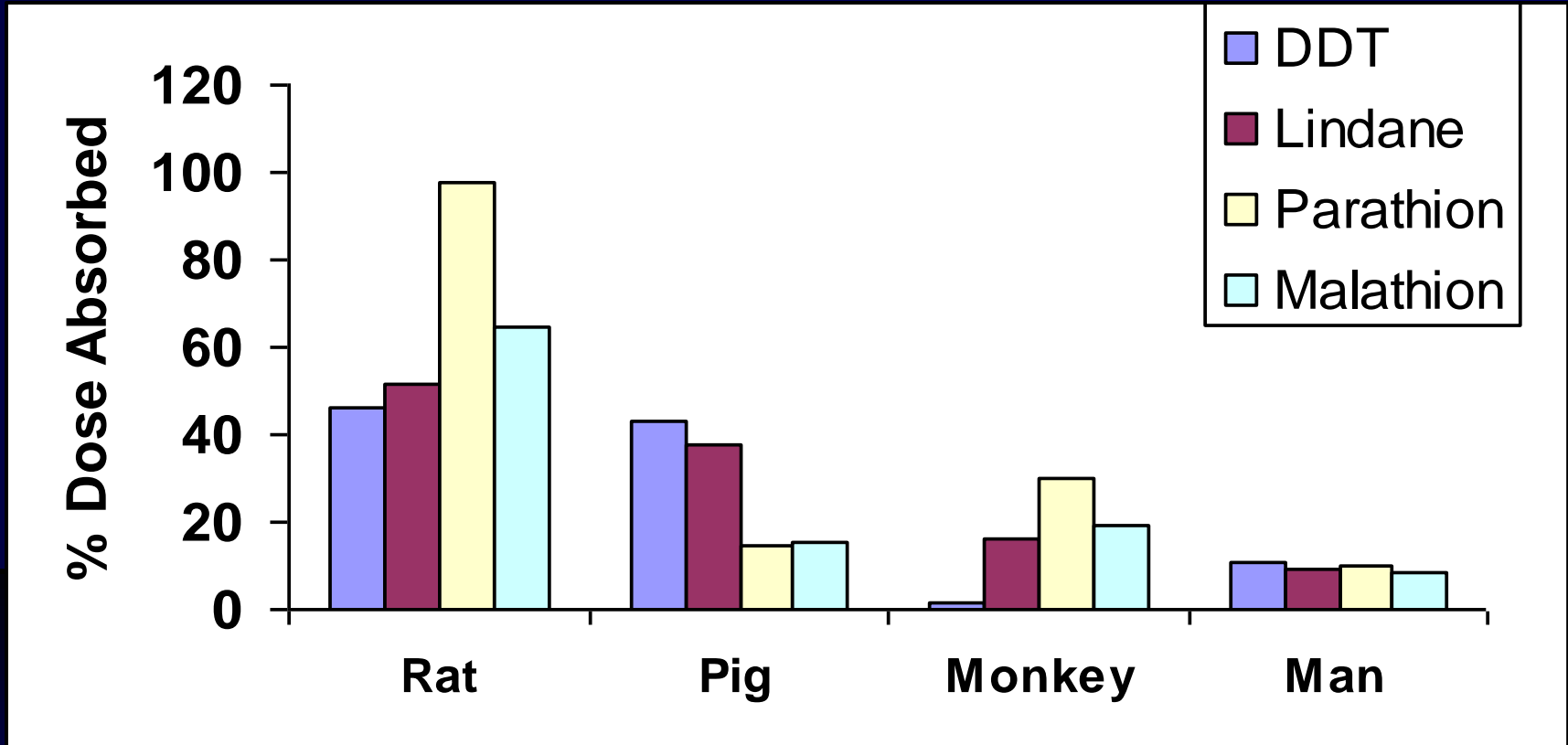
Human abdominal skin, 150X



Pig abdominal skin, 150X

Species Differences in In Vivo Dermal Absorption

(from Principles And Methods of Toxicology)



Which species is predictive of human dermal absorption????

- **Dermal Absorption Basics**
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- **Once absorbed, what are the adverse effects of insecticides in veterinary species?**
- **Can there be Residues in meat and milk if livestock species are treated with these drugs?**
- **FARAD Cases and their resolution**
- **Future and Challenges**

Adverse Effects of Ectoparasiticides

- Occasional to rare in companion animals
 - Idiosyncratic reactions or not reading/following the label
- Rare in food animals
- Reason: These drugs target receptors in the insect and are more selective for these receptors in insects than vet. spp and humans



Adverse Effects of Ectoparasiticides

Active Ingredients

- Organochlorines
- **Organophosphates**
- Pyrethrins
- Neonicotinoids
- Fipronil
- Macrolide Endectocides,
- Growth inhibitors

Comparative Toxicity

- Yes
- Very Toxic !!!
- Yes
- No
- No
- No (except some breeds)
- Harmless



Adverse Reactions to OPs

- **Animals vary in response to insecticides**
 - age (young vs. adult), health, stress, species (cats are sensitive)
- **Toxicity**
 - muscarinic and nicotinic effects
 - some OPs cause OPIDN (clinical signs delayed 7 - 21 days)
 - highly toxic to birds, fish, aquatic invertebrates, and honeybees.
 - **Brahman cattle, greyhounds, and cats are sensitive to OPs**
 - **being lipophilic, may get residues in meat and milk**
 - famphur & fenthion = 35 & 45 days meat WDT (No dairy approval)
 - But coumaphos (Co-Ral) has no meat or milk WDT

Adverse Reactions to OPs

All related to Overstimulation of ACh Receptors

muscarinic acetylcholine receptors symptoms of :

Visual disturbances (miosis),

Bronchoconstriction, increased bronchial secretions,

Increased salivation, lacrimation, sweating, peristalsis, and urination

nicotinic acetylcholine receptors in the central nervous system:

anxiety, headache, convulsions, ataxia, depression of respiration and circulation, tremor, general weakness, and potentially coma.

At the neuromuscular junction:

muscle weakness, fatigue, muscle cramps, and paralysis

Adverse Reactions to Pyrethrins

- **more selective for insects, and safer than OPs & Carbamates**
- most common way cats can be poisoned by pyrethrins is by inappropriate application of dog flea and tick medications in cat
- **clinical signs include nerve and muscular disorders**
 - **Type I compounds (permethrin) → rapid onset of hyperactivity (as DDT)**
 - **Type II compounds (fenvalerate) → serious side effects at low doses**

Adverse Reactions to Pyrethroids

Onset of clinical signs is usually within a few hours of exposure but may be delayed up to 24 hours

- Profuse drooling
 - Vomiting
 - Tremors
- Hyperexcitability
 - Agitation
 - Seizures
 - Weakness
- Difficulty breathing

- Dermal Absorption Basics
 - How are these drugs absorbed?
- Once absorbed, what are the adverse effects of insecticides in veterinary species?
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Why should I care about residues?



Danger to consumer



Lost milk product (\$6000 to \$80,000)

CONSENT DECREE SIGNED IN DRUG RESIDUE CASE



On July 5, 1995, a Consent Decree of Permanent Injunction was signed by David L. Hogan, owner of Hogan's Misty Meadow Dairy, Tillamook, Oregon. This dairy is primarily a producer of fluid milk, with a producing herd of 700 cows. In addition, the

farm produces bull calves which are sold for slaughter or for further raising and then slaughter for human food.

The injunction action against Mr. Hogan was based on 16 residue incidents in veal during the period from March 1990 through June 1994. The illegal drug residues involved included streptomycin, neomycin, gentamicin, and oxytetracycline. The Consent Decree permanently restrained and enjoined Mr. Hogan from introducing or delivering for introduction into interstate commerce any cattle intended to

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Regulatory problems



Lost cull price (\$500)

Why should I care?

Can people really get sick from residues?

- Yes!
- In one 6 month period in 1993 more than 1,200 hospitalizations and 3 deaths in France and Spain were reported to have resulted from eating beef livers contaminated with the illegal growth promotant clenbuterol.
- 6/38 animals tested + at OK state fair in 1995.
- Vet: 8 months & \$80,000 for smuggling it into US in 1999.

ILLEGAL USE OF CLENBUTEROL IN FOOD ANIMALS

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By Dr. William C. Keller

As we mentioned in the last issue of the *FDA Veterinarian*, FDA is investigating the illegal use of the drug, clenbuterol, in animals used for food, particularly animals being prepared for livestock show competition. The purpose of this article is to illustrate the potential consequences of illegal drug use in food animals by describing an outbreak of clenbuterol-related drug residue poisoning, and to explain the scientific basis for the Center for Veterinary Medicine's (CVM) particular concern for illegal use of clenbuterol in food producing animals. The following description of an outbreak of clenbuterol residue toxicity demonstrates the potential public health consequences of illegal use of drugs in animals used for food.

Numerous cases of illness, which appeared to be due to food poisoning,

or in feed to animals, and of apparent therapeutic or production value in animal husbandry. Based on these criteria, it was suspected that illegal use of a β agonist in cattle was responsible for the poisoning outbreak. Prompt follow-up on a number of patients had allowed the investigators to collect samples of the suspected food, as well as urine samples from the individuals. Analysis of these samples revealed that a β agonist, clenbuterol, was present at levels of 2.4 ppb in patients' urine and 160-291 ppb in beef liver samples. This confirmed the investigators' suspicions that an illegal animal drug residue present in liver had produced the outbreak of food-borne poisoning.

"Analysis of these samples ... confirmed the investiga-

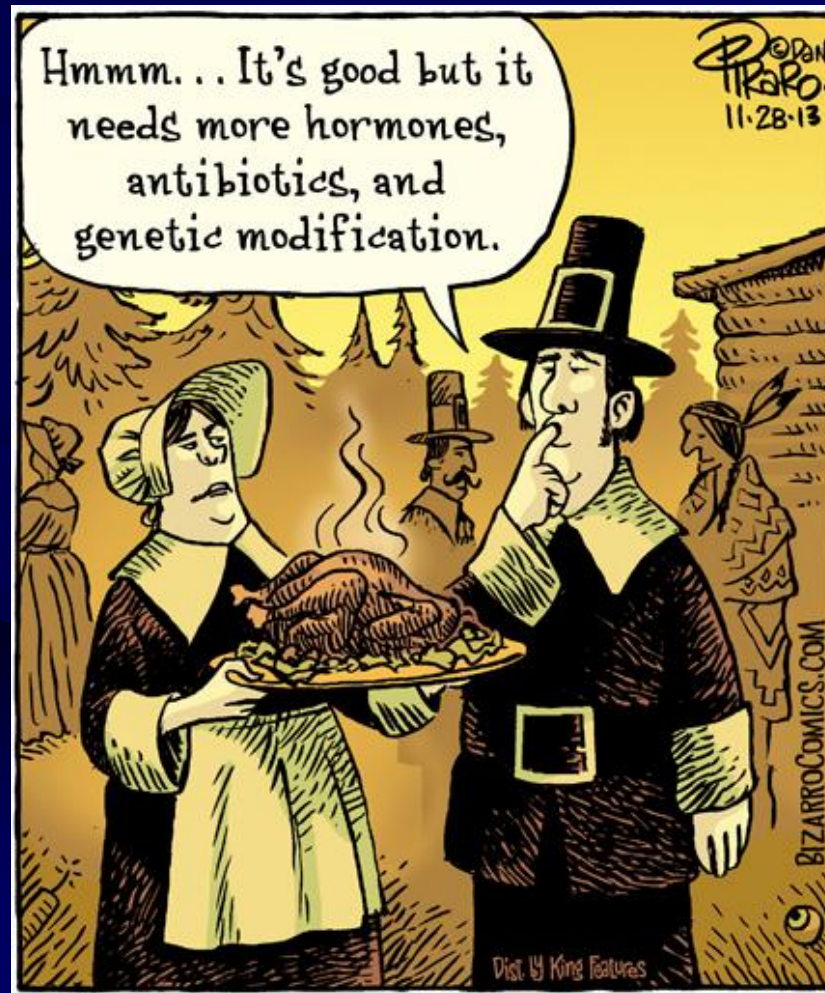


Why should I care?

Perceptions and not science are often the drivers

evidenced by growth of the organic food industry

“dose makes the poison” is ignored



Potential Sources of Residues

- Not following the label WDT
- Extra-label use without using an appropriate WDT
- Environmental contamination
- Contamination of feed
- Emergency treatment of wounded and sick animals
- Slaughter of unidentified animals



Relevant FARAD Cases

Can these Ectoparasiticide drugs be used in an extralabel manner?

Yes, for FDA approved drugs

NO, for EPA Registered products

Real Case: Cydectin

- Background

- A goat farmer found that oral Ivomec was not reducing parasitism in his goat herd, and he decided to dose the goats orally with Cydectin.
- He also treated with 4 X the approved cattle dose.

- Questions:

- Is this approved or extra-label use of this drug?
- Can we use the approved meat WDT for cattle of Zero days if we treat goats topically or orally?

Real Case: Cydectin

- Answer

- Cydectin is approved for topical use in cattle NOT goats.
- There is no approval for ORAL use in cattle, but if it was, there will be a significant WDT for cattle destined for slaughter. i.e.,
NOT ZERO DAYS !!!

Therefore, expect to with-hold meat goats for at least several weeks before slaughter if goats are treated orally with this drug.

Real Case: Heptachlor

Two incidents of mass contamination of livestock.

Case confined to Hawaii in 1982:

EPA granted an emergency exemption to pineapple growers to use heptachlor

Dairy cattle fed contaminated pineapple green-chop byproducts.

Widespread contamination of the Hawaiian milk supply and losses estimated at millions dollars .

Ethanol plant in SW Missouri routinely purchased surplus seed grain that had been treated with insecticides and fungicides.

Spent distiller's grains were used in the manufacture of animal feeds.

Heptachlor residues were detected in milk samples from > 50 dairies.

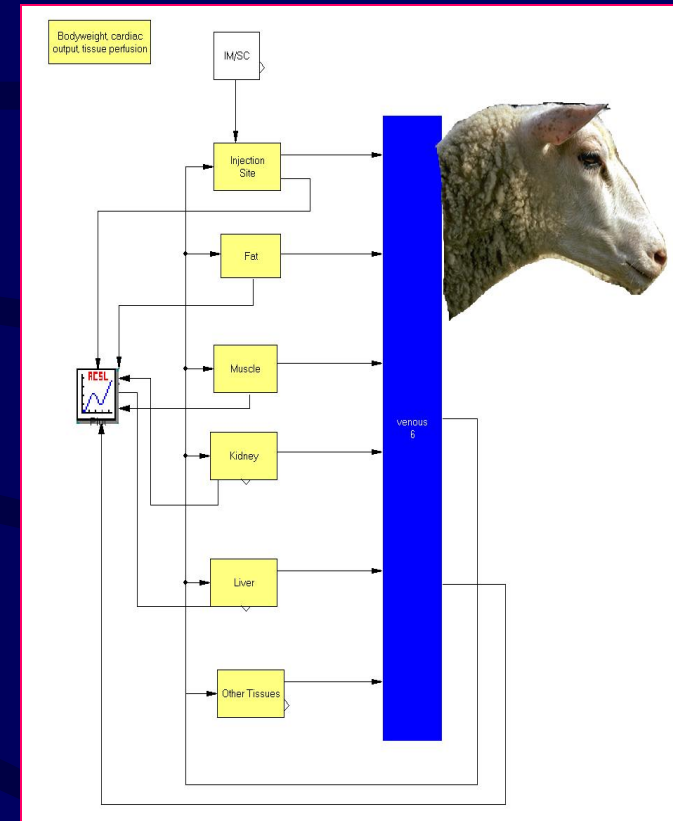
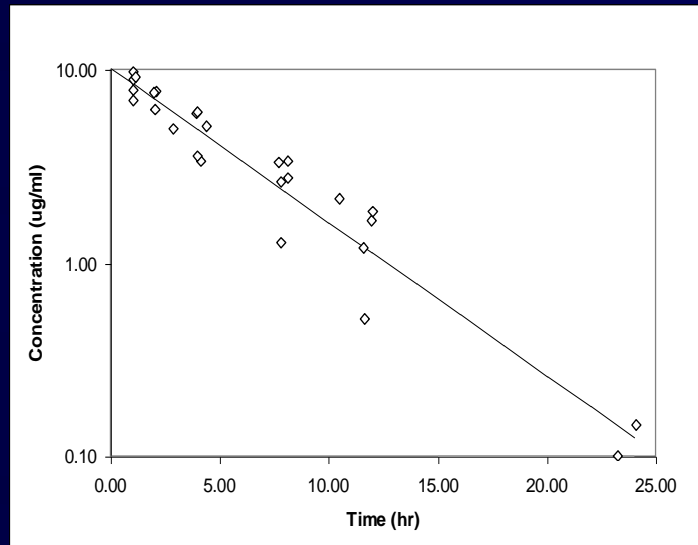
Several beef and swine herds also were quarantined.

Losses undoubtedly would have totaled several million dollars if FARAD had not provided withdrawal time information.

What about practical approaches for managing a chemical contaminant exposure in livestock??

- Melamine
- PCBs
- Petrochemicals
- Other POPs
- Solvents
- etc

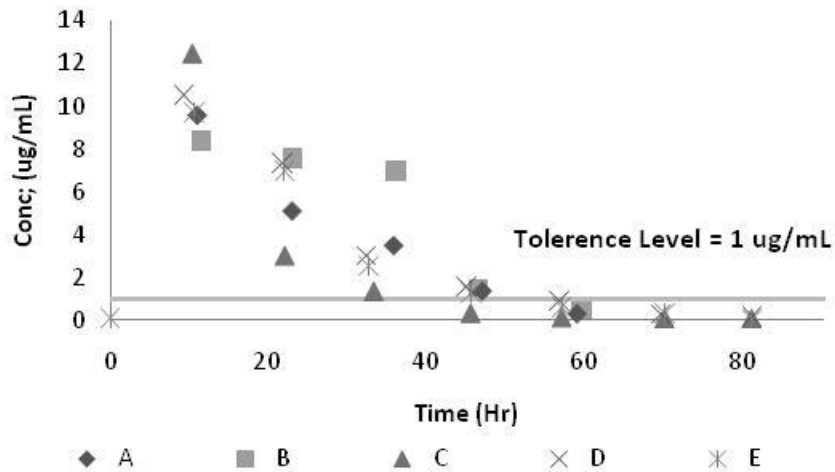
Melamine Exposure in swine: Use of PBPK Modeling



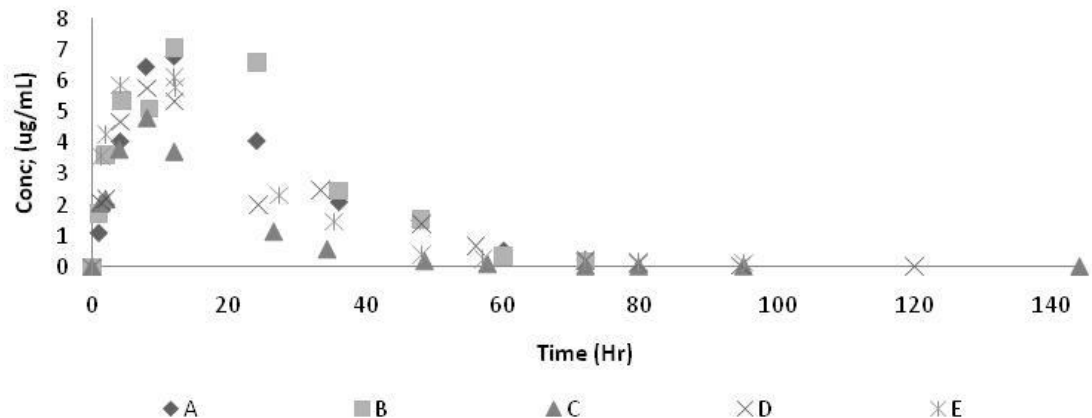
| | $T_{1/2}$ | CI | V_{ss} | AUC | K_{el} | MRT |
|------|-----------|-----------|----------|----------------|----------|------|
| | (hr) | (L/hr/kg) | (L/kg) | hr* μ g/ml | 1/hr | (hr) |
| Mean | 4.07 | 0.11 | 0.61 | 59.26 | 0.18 | 5.87 |
| SE | 0.39 | 0.01 | 0.04 | 5.89 | 0.02 | 0.56 |

When is it safe to use the milk or meat from dairy animals exposed to melamine??

Melamine Concentration in Milk

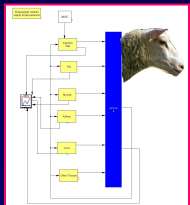


Melamine Concentration in Plasma



Summary & Challenges

- These drugs/insecticides can be absorbed across skin to work locally or systemically.
 - » (Formulation Dependent !!!)
- Once absorbed, any adverse effects are usually associated with very few drug classes (OPs and Pyrethroids).
- Veterinarian, Client, and Patient can be affected
- Drug/Insecticide Residues in meat and milk can occur in livestock treated with these drugs if used Extralabel !!
- The FARAD National Program uses its PK database and novel Pharmacometrics methods in risk management of challenges associated with drug and pesticide exposure



The End

